

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
20 July 2006 (20.07.2006)

PCT

(10) International Publication Number  
**WO 2006/075184 A1**

(51) International Patent Classification:  
*A61M 15/00* (2006.01)

(21) International Application Number:  
PCT/GB2006/000141

(22) International Filing Date: 16 January 2006 (16.01.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0500677.0 14 January 2005 (14.01.2005) GB

(71) Applicant (for all designated States except US): **BRI-TANNIA PHARMACEUTICALS LIMITED** [GB/GB]; 41-51 Brighton Road, Redhill, Surrey RH1 6YS (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **WOODCOCK, Derek, Alan** [GB/GB]; 24 Shrublands Road, Berkhamsted, Hertfordshire HP4 3HX (GB). **PYNN, Christopher** [GB/GB]; 27 Silchester Road, Pamber Heath, Tadley, Hampshire RG26 3ED (GB). **THOMPSON, James** [GB/GB]; Lines Cottage, 36 Broadway, Old Amersham, Buckinghamshire HP7 0HJ (GB).

(74) Agents: **STONER, Patrick** et al.; Mewburn Ellis LLP, York House, 23 Kingsway, London, Greater London WC2B 6HP (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

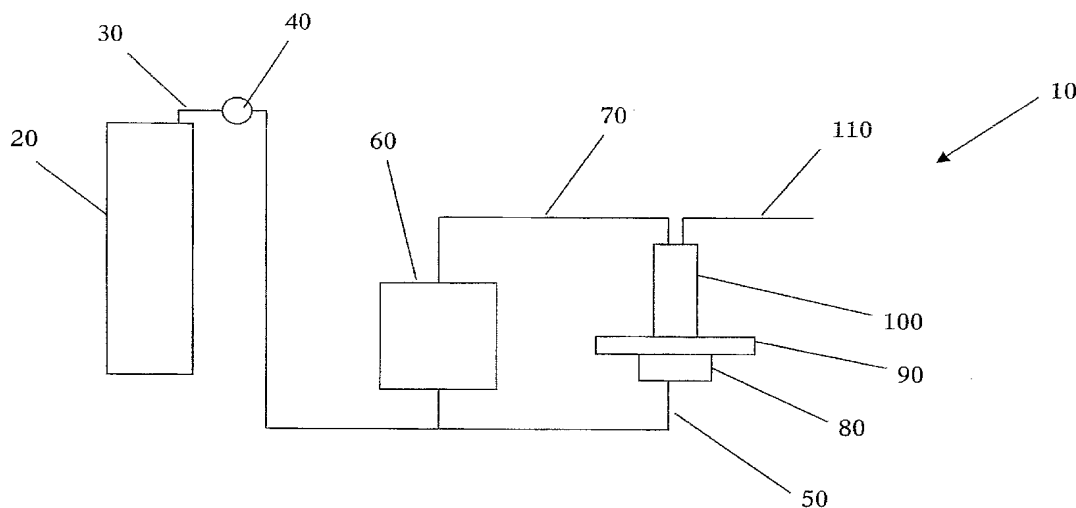
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: APPARATUS AND METHODS FOR PROVIDING DRY POWDER MEDICAMENT FOR INHALATION



(57) Abstract: The application describes apparatus and methods for delivering a powdered medicament for inhalation. The medicament is put in a receptacle (100) on a vibration generator (80) operated by fluid pressure, e.g. by means of an eccentric rotor. A flow of gas from a supply (20) is passed into the receptacle (100), producing in concert with the vibration an aerosol which passes out of the receptacle and along a tube (110) to be inhaled by the patient. Both the gas flow supply and vibration may be subject to the operation of a control unit (60), which may time the production of the aerosol according to a patient's breathing cycle, e.g. as part of a ventilator system.

WO 2006/075184 A1

APPARATUS AND METHODS FOR PROVIDING DRY POWDER MEDICAMENT  
FOR INHALATION

The present invention is concerned with a dry powder inhaler which typically generates an aerosol of powder particles. In particular, the dry powder inhaler may be used for continuous delivery of a medicament to a patient without requiring activation by the patient.

Typically when a patient's medical condition requires continuous administration of a medicament, the equipment generally used to administer the medicament is a nebuliser. Nebulisers work by generating a fine aerosol of liquid particles from a solution of a medicament. This aerosol may be administered to a patient via a mouthpiece, facemask or via an endotracheal tube for a ventilator.

The problem with a nebuliser is that it is not suitable for administering a medicament which cannot be formulated in liquid form. In addition the efficacy of nebulisers is reduced when included in ventilator circuits as the endotracheal tube acts in part as a block to aerosol deposition. Such a system generally comprises a respirable air generator connected to an endotracheal tube. A nebuliser is used with such a system by connecting it to the endotracheal tube. There is the problem that some of the aerosolised medicament is not inhaled by the patient. This is because where there are bends in the endotracheal tube, at least some of the aerosolised medicament impacts the tube, forming a liquid deposit. The use of a nebuliser in conjunction with a ventilator will frequently require disrupting the ventilator circuit in order to insert the nebuliser. While this is standard practice in many units, it is not entirely without risk. The only alternative to this is to take a patient off an automated ventilator whilst a medicament is administered but this is clearly dangerous for the patient.

To administer a powdered medicament, a dry powder inhaler (DPI) is

typically used. In a DPI device, no propellant is used but instead the device relies upon a burst of inspired air drawn through the unit by the patient to aerosolise the medicament. These devices suffer from the problem that they require activation by the patient and are unable to  
5 supply an aerosolised medicament continuously.

A way of ameliorating these problems has been sought.

In one aspect the present invention provides a delivery system for a  
10 powdered medicament comprising:

a vibration generator, preferably powered by a pressurised fluid supply;

a gas supply; and

a receptacle for a powdered medicament which receptacle has an  
15 inlet connected to the gas supply;

wherein the receptacle is connected to, e.g. supported by, the vibration generator, for the vibration and the supply of gas to the receptacle to cause a powder in the receptacle to fluidise in use, generating an aerosol.

20 One advantage of the present invention is that the invention provides a simple delivery system for a powdered medicament which can be used to provide a continuous supply of a medicament. Thus the system according to the invention provides a way of delivering a powdered medicament in a similar manner to how a nebuliser delivers a liquid medicament.

25

A further advantage of the invention is that the aerosol is generated by fluid pressure. Thus in a hospital environment where pressurised cylinders of gases such as oxygen or air are commonly available, the system is easy to operate at a minimal expense.

30

A further advantage of the present invention is that it is suitable for administering cohesive powders. Pumactant which is a blend of

dipalmitoylphosphatidylcholine (DPPC) and phosphatidylglycerol (PG) (DPPC:PG 7:3), is very cohesive due to its low particle size, high moisture affinity and predominantly amorphous structure. It has surprisingly been found that the present invention is suitable for  
5 administering a respirable dose of pumactant.

Any known vibration generator, e.g. pneumatic, may be used in the present invention. For ease of use, the vibration generator is preferably compact. Preferably the vibration generator comprises an asymmetrically weighted  
10 (eccentric) rotor. Such a rotor may be driven by piston or turbine, preferably turbine.

The system preferably comprises a control unit for controlling the gas supply such that the gas supply is an even supply of gas without  
15 fluctuation in the flow rate or pressure of the gas. The control unit is preferably adapted to generate a pulsed gas supply, e.g. so that the flow of gas is intermittent. The control unit is preferably further adapted to monitor the pressure output and duration of the pulsed gas supply.

The control unit may also control the vibration generator in  
20 order that the generation of vibration may be timed to be at the same time or shortly before the flow of gas from the control unit.

The gas used in the gas supply is preferably carbon dioxide, nitrogen, air, or a halocarbon (e.g. a fluorocarbon such as HFA-134a or HFC-227);  
25 more preferably the gas is carbon dioxide. Where the powdered medicament is hygroscopic or otherwise sensitive to water, the gas supply is preferably a supply of dry gas. Alternatively, the gas supply preferably passes a dryer, such as exposure to a body of a desiccant material, to dry the gas before it reaches the  
30 receptacle. Any known desiccants used to dry a supply of gas may be used, such as activated alumina, a silica gel or a molecular sieve.

The receptacle has an outlet from which the aerosol is

discharged. The outlet is preferably connected to an outlet tube. The outlet tube may be provided with a connector means suitable for linking the gas outlet with a ventilator or other assisted breathing system used in a hospital environment. Alternatively, the outlet tube may be provided in the form of an endotracheal tube. As a further alternative, the outlet tube may be provided with a mask to aid a patient to inhale the aerosol. The outlet tube generally has a proximal end and a distal end. The proximal end of the outlet tube is connected to the outlet of the receptacle. The distal end of the outlet tube is preferably provided with a one way valve to prevent contamination of the receptacle, e.g. between pulses of a pulsed gas supply.

Where the system of the invention is used in association with a ventilator, the control unit may be functionally linked to the ventilator, e.g. electronically by an electric cable or wirelessly. This is in order that the control unit can time the supply of gas such that the aerosol produced by the system of the invention at the distal end of the outlet tube coincides with the respirable air generated at the corresponding point of the endotracheal tube of the ventilator such that the patient inhales the aerosol into his or her lungs. Optionally the control unit may also control the vibration generator such that the vibration of the receptacle is also timed to coincide with the inspiratory cycle of the ventilator.

According to a further aspect of the present invention there is provided a method of dispensing a powdered medicament to a patient in need of such treatment which method comprises the steps of:

- (a) providing a receptacle containing the powdered medicament;
- (b) vibrating the receptacle using a vibration generator;
- (c) passing a stream of gas through the receptacle to generate an aerosol of the powdered medicament;

wherein the vibration generator is preferably powered by a pressurised fluid supply as above.

The steps of this method may be performed sequentially, or steps (b) and (c) may be carried out simultaneously.

- 5 The method preferably includes a further step (d) of discharging the aerosol preferably through an outlet tube as described above.

Step (c) preferably comprises passing a controlled pulse of gas through the receptacle to generate an aerosol of the powdered medicament. The  
10 pulse of gas preferably has controlled duration and pressure. It is preferably a pulse of gas having an even flow.

Where the patient is using an assisted breathing system which generates respirable air for the patient, step (c) preferably comprises producing a series of pulses of gas such that the aerosol is generated and supplied through an outlet at substantially the same time as or in synchronicity with the generation of respirable air by the assisted breathing system.

The receptacle containing the medicament can be any suitable packaging container, for example, a glass or plastic vial or a blister pack. Typically  
20 the opening of the receptacle is sealed to preserve sterility of the powder and/or to avoid water adsorption.

The receptacle may contain a single dose of powder for one-time use, or sufficient powder for several doses. It preferably contains from 1 to 20  
25 doses, each containing from 1 to 20mg of powder; e.g. 10 or 20 doses of 10mg. or 10 or 20 doses of 2mg. The medicament is preferably in the form of a respirable powder.

Preferably the medicament is in the form of a respirable powder.  
30 Preferably the medicament is in the form of powder particles having a mass median aerodynamic diameter (MMAD) measured by laser diffraction of less than 50 $\mu$ m, preferably less than 20 $\mu$ m, more preferably

less than 10 $\mu$ m, most preferably less than 5 $\mu$ m, particularly preferably from 1 $\mu$ m to 5 $\mu$ m.

5 The system of the invention can be used to administer any medicament suitable for administration by inhalation such as a SAPL (surface active phospholipid) composition, such as pumactant; a bronchodilator (a  $\beta_2$ -agonist or an anti-cholinergic agent), a steroid (such as budesonide), a mucolytic agent, an enzyme (e.g.  $\alpha$ 1-trypsin), a chemotherapy agent, an immune suppressant (e.g. cyclosporine), a systemic treatment (such as  
10 insulin).

The invention is illustrated by way of example by the Figures of the accompanying drawings in which:

15 **Figure 1** is a schematic view of a system according to the invention;

**Figure 2** is a cross-sectional view of a vibration generator suitable for use in a system according to the invention;

20 **Figure 3** is a schematic view of a system according to the invention connected to a ventilator unit; and

**Figure 4** shows a schematic view of an output tube fitting.

25 **Figure 1** shows a system 10 embodying the invention having a pressurised gas cylinder 20 containing carbon dioxide, a gas supply line 30 leading from the cylinder 20 to a gas pressure regulator 40. The gas pressure regulator 40 is connected to a control unit 60 and a vibration  
30 generator 80 by gas supply lines 50.

A table 90 is supported by the vibration generator 80. A receptacle 100 is placed on the table 90. The receptacle has a gas inlet line 70 which is connected to the control unit 60 and a gas outlet line 110. The receptacle contains the powder to be aerosolised.

5

Control unit 60 controls the duration and flow of pulses of gas from cylinder 20. Control unit 60 comprises a solenoid valve with electronic flow control (not shown). The solenoid valve of the control unit 60 is a high purity, grease-free valve. The output pressure of the control unit is from 2 to 100 kPa. Optionally, the control unit may also control the vibration generator 80 in order that the generation of vibration may be timed to be at the same time or shortly before the flow of gas from the control unit.

15 As an alternative to the embodiment shown in Figure 1, the table 90 can be formed by the vibration generator 80 such that the receptacle 100 is placed directly on the vibration generator. Also pressurised gas cylinder 20 could be replaced by two pressurised gas cylinders, one connected to the vibration generator 80 and the other connected to the control unit 60.

20

Vibration generator 80 is shown in more detail in Figure 2. It comprises a body 200 generally formed from a metal casting or extrusion; the body 200 has air inlet and outlet channels. Body 200 supports a turbine wheel 210 which has paddles (not shown) such that in use the turbine wheel 210 is caused to rotate by the application of gas pressure from the cylinder 20.

The turbine wheel 210 has high density sections 220 forming positive elements. The turbine wheel 210 forms cavities 230 which are negative elements. Rotation of the turbine wheel 210 causes the table 90 and receptacle 100 to vibrate by the centrifugal force of the positive and

30



negative unbalance elements in the turbine wheel 210. The turbine wheel is supported on two pre-lubricated matched sealed bearings (not shown).

In use, the gas cylinder 20 and regulator 40 are adjusted to supply a gas pressure of about 3 Bar. This activates vibration generator 80 which causes a powder (not shown) in the receptacle to fluidise by vibrating the receptacle at a rate of about 12,000 vibrations per minute. Control unit 60 is then activated to supply a flow of gas to the receptacle 100 at a pressure of about 1 Bar through gas inlet line 70 so that an aerosol of fluidised powder is emitted from the receptacle 100 through gas outlet line 110.

In Figure 3, the system 10 of the invention is shown in use, connected to a ventilator 130. Like numerals are used in Figure 3 to describe like features in the earlier Figures. In particular, the control unit 60 is in electronic communication with the ventilator 130 which is indicated by 120. The electronic communication is shown in the form of an electric cable but as an alternative may be wireless electronic communication. The ventilator generates respirable air through endotracheal tube 140,160. The outlet tube 110 is connected to endotracheal tube 140 at connector 150. The distal end of the outlet tube 110 at the connector 150 is provided with a one way valve (not shown). This is because the respirable air generated by the ventilator is usually humid respirable air. The one way valve prevents flow of the respirable air into the receptacle 100.

The control unit 60 is in electronic communication with the ventilator in order that the flow of gas from the control unit can be timed such that the outlet tube 110 provides an aerosol of powdered medicament at connector 150 at a time to coincide with the production of respirable air by the ventilator.

As an alternative to the embodiment shown in Figure 3, the outlet tube 110 does not connect to the endotracheal tube 140,160 but is instead in the form of an endotracheal tube itself. The outlet endotracheal tube 110 is then arranged in parallel with the ventilator endotracheal tube 140,160.

- 5 In this arrangement, the ventilator and control unit are arranged to generate respirable air and an aerosol, respectively, at the distal ends of the endotracheal tubes 140,160 and 110 at about the same time. This is to ensure that the aerosol is produced when the patient is inhaling.

- 10 Figure 4 shows an alternative embodiment to Figure 3 where the outlet tube 110 of the system 10 is connected to a inhalation mask 300 which is suitable for a patient to wear on their face to cover their mouth and nose such that they can inhale the aerosol generated by the system 10.

## CLAIMS

1. A delivery system for a powdered medicament comprising:  
a vibration generator which is powered by a pressurised fluid  
5 supply;  
a gas supply; and  
a receptacle for a powdered medicament which receptacle has an  
inlet connected to the gas supply;  
wherein the receptacle is connected to the vibration generator such that  
10 the vibration and the supply of gas to the receptacle cause the powder in  
the receptacle to fluidise generating an aerosol.
2. A system according to Claim 1 comprising a control unit  
programmed to control the gas supply to generate a timed series of  
gas flow pulses.  
15
3. A system according to Claim 1 or 2 wherein the vibration  
generator comprises an asymmetrically weighted rotor.
4. A system according to Claim 1, 2 or 3 in which a control unit  
is operable to control the gas supply to give an even supply of  
20 gas, without fluctuation in flow rate or pressure of the gas when  
flowing.
5. A system according to any one of the preceding claims wherein  
a control unit is operable to control the vibration generator in  
order that the generation of vibrations is timed to be in register  
25 with, e.g. at the same time as or shortly before, a period of gas  
supply from the control unit.
6. A system according to any one of the preceding claims wherein  
a control unit is further adapted to monitor the pressure output  
and duration of the gas supply.

7. A system according to any one of the preceding Claims wherein the gas used in the gas supply is carbon dioxide, nitrogen, air, or a halocarbon; preferably the gas is carbon dioxide.

8. A system according to any one of the preceding Claims wherein the gas supply is a supply of dry gas.

9. A system according to any one of the preceding Claims wherein the receptacle has an outlet from which the aerosol is discharged which outlet is connected to an outlet tube.

10. A system according to Claim 9 wherein the outlet tube is provided with a connector suitable for linking the gas outlet with an assisted breathing system or with an inhalation mask.

11. A system according to Claim 9 wherein the outlet tube is in the form of an endotracheal tube.

12. A system according to any one of Claims 9 to 11 wherein the distal end of the outlet tube is provided with a one way valve to prevent contamination of the receptacle.

13. A system according to Claim 10 wherein the system comprises a control unit as defined in any one of Claims 3 to 6 wherein the control unit is adapted to communicate with an assisted breathing system such that the discharge of the aerosol can be timed by the control system to coincide with production of respirable air by the assisted breathing system.

14. A system according to any one of the preceding claims wherein the

medicament is in the form of a respirable powder, preferably the medicament is in the form of a powder having a mass median aerodynamic diameter (MMAD) measured by laser diffraction of less than 50 $\mu$ m, preferably less than 20 $\mu$ m, more preferably less than 10 $\mu$ m, most  
5 preferably less than 5 $\mu$ m, particularly preferably from 1 $\mu$ m to 5 $\mu$ m.

15. A system according to any one of the preceding claims wherein the receptacle contains from 1 to 20 doses, each containing from 1 to 20mg of powder.

10

16. A method of dispensing a powdered medicament to a patient in need of such treatment which method comprises the steps of:

- (a) providing a receptacle containing the powdered medicament;
  - (b) vibrating the receptacle using a vibration generator;
  - 15 (c) passing a stream of gas through the receptacle to generate an aerosol of the powdered medicament;
- wherein the vibration generator is powered by a pressurised fluid supply.

17. A method according to Claim 16 wherein the steps of the method  
20 of the invention are performed sequentially.

18. A method according to Claim 16 wherein steps (b) and (c) are carried out simultaneously after step (a).

25 19. A method according to any one of Claims 16 to 18 which includes a further step (d) of discharging the aerosol preferably through an outlet tube as claimed in any one of Claims 9 to 11.

20. A method according to any one of Claims 16 to 19 wherein step (c)  
30 comprises passing a controlled pulse of gas through the receptacle to generate an aerosol of the powdered medicament; the pulse of gas preferably has controlled duration and pressure.

21. A method according to Claim 20 wherein the patient is using an assisted breathing system which generates respirable air for the patient and wherein in step (c) the pulse of gas is controlled such that the aerosol  
5 is generated at substantially the same time as the assisted breathing system generates the respirable air.

22. A method according to any one of Claims 16 to 21 wherein the medicament is in the form of a respirable powder; preferably the  
10 medicament is in the form of powder particles having a mass median aerodynamic diameter (MMAD) measured by laser diffraction of less than 50 $\mu$ m, preferably less than 20 $\mu$ m, more preferably less than 10 $\mu$ m, most preferably less than 5 $\mu$ m, particularly preferably from 1 $\mu$ m to 5 $\mu$ m.

15 23. A method according to any one of Claims 16 to 22 wherein the gas is carbon dioxide, nitrogen, air, or a halocarbon; preferably the gas is carbon dioxide.

24. A method according to any one of Claims 16 to 23 wherein the  
20 stream of gas is a dry stream of gas.

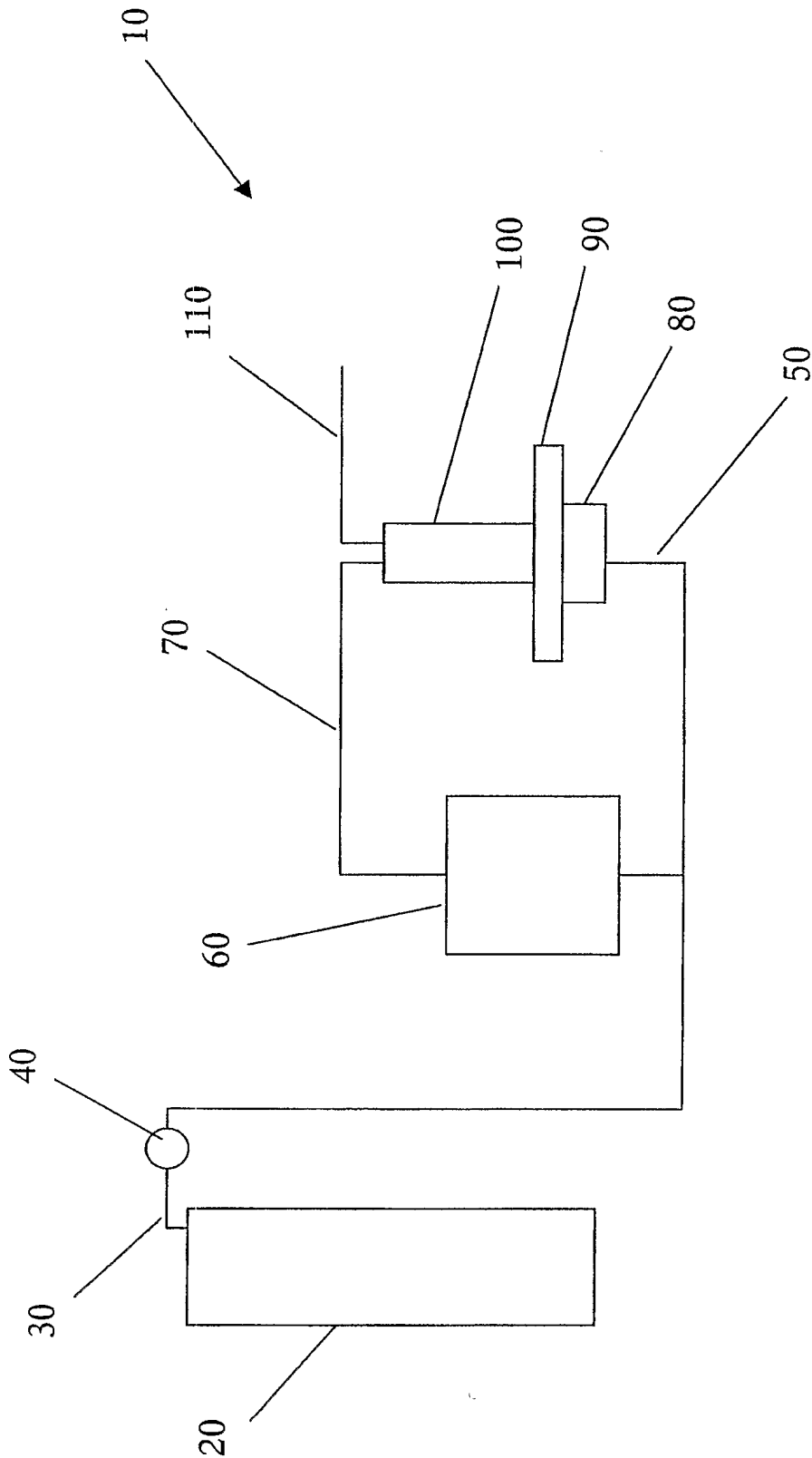


FIGURE 1

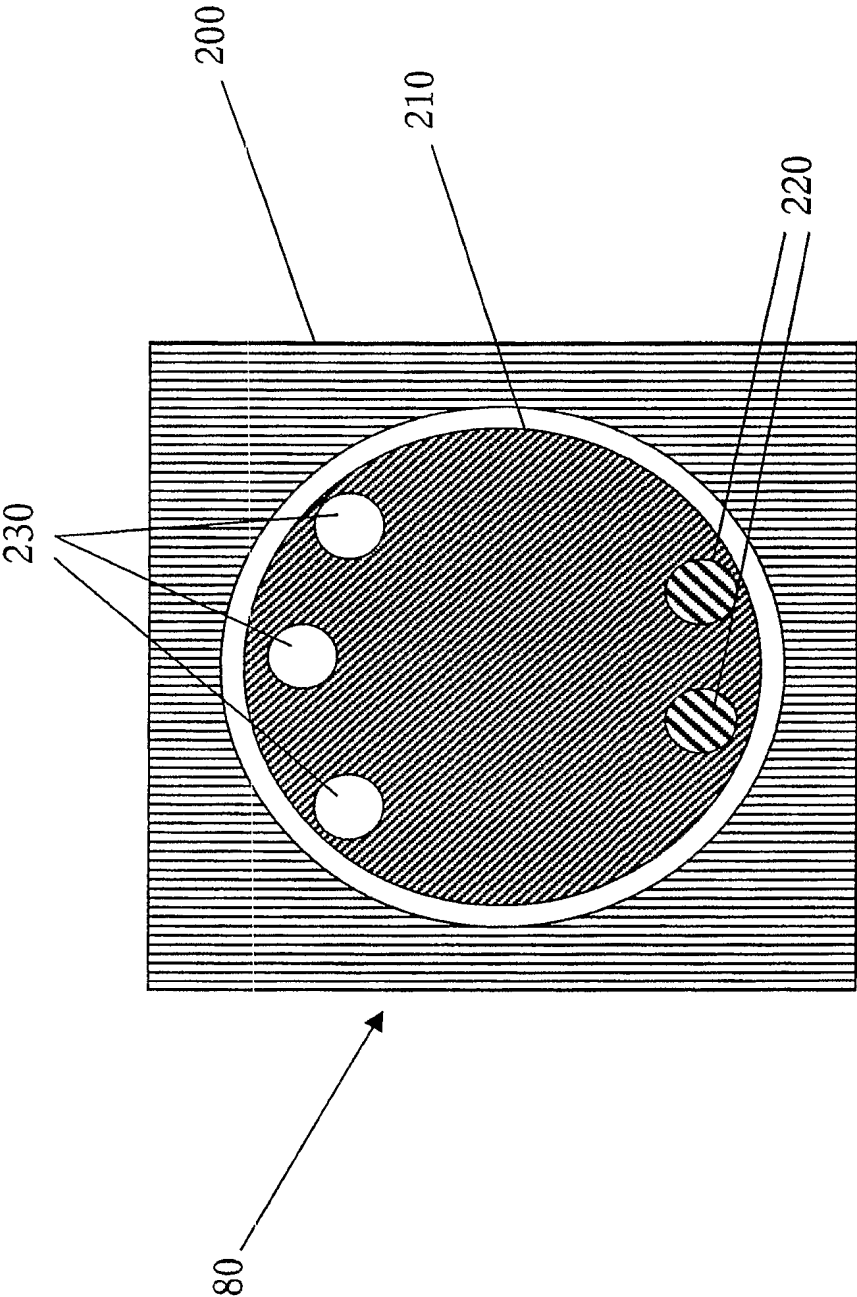


FIGURE 2



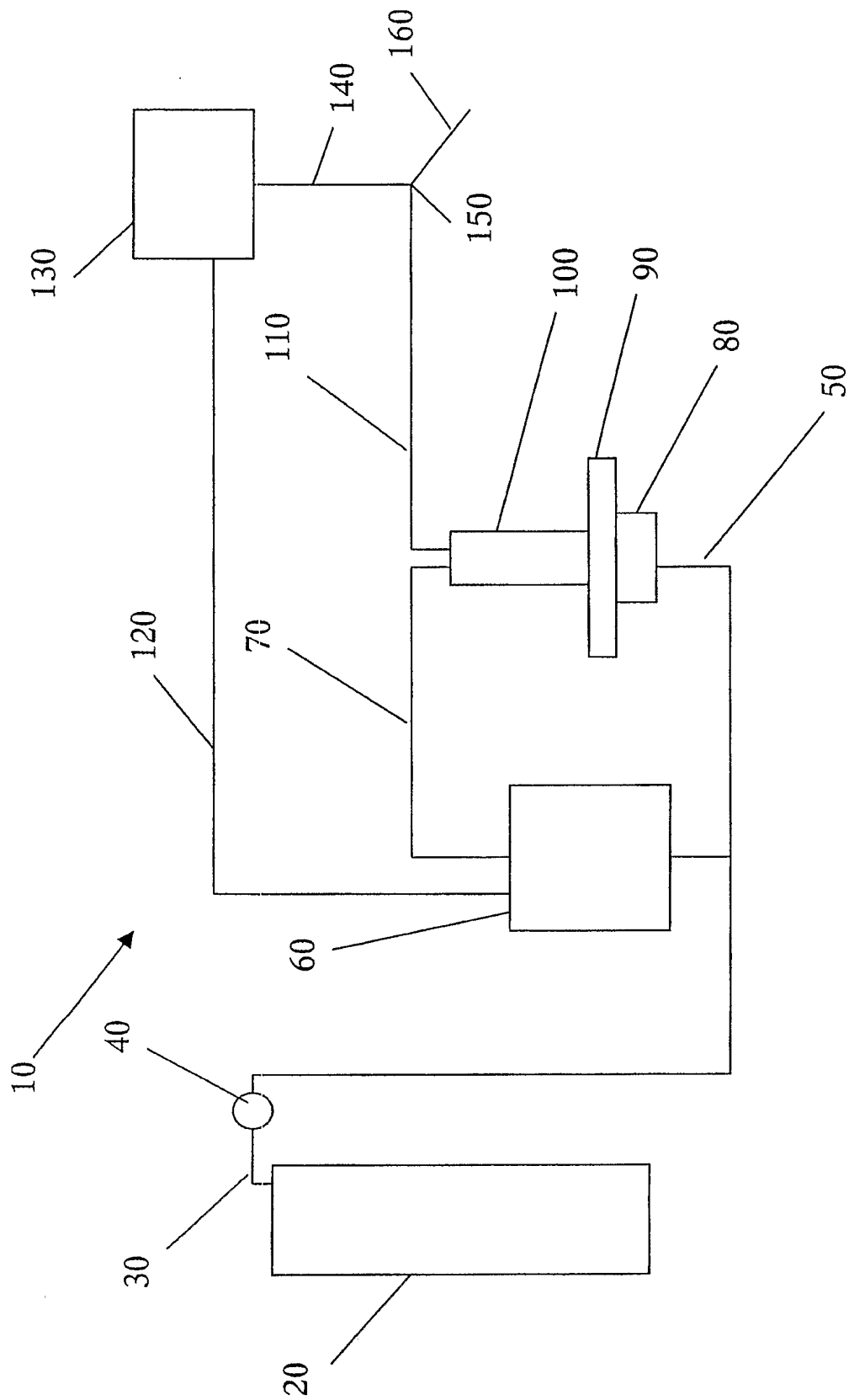


FIGURE 3

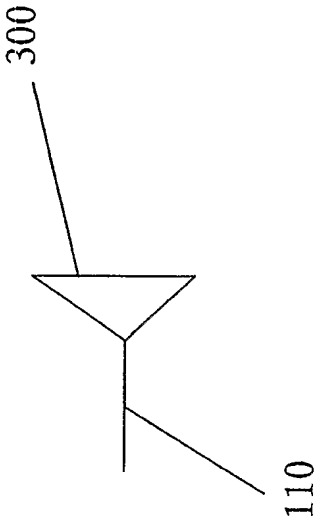


FIGURE 4

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2006/000141

A. CLASSIFICATION OF SUBJECT MATTER  
INV. A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 809 084 A (HANSEN L,US) 7 May 1974 (1974-05-07) the whole document	1,2,4-15
X	US 2002/088462 A1 (GENOVA PERRY ET AL) 11 July 2002 (2002-07-11) the whole document	1,2,4-15
X	US 3 653 380 A (LLOYD FRANK HANSEN) 4 April 1972 (1972-04-04) column 1, line 36 - column 2, line 5 column 2, line 61 - column 4, line 10 claims 1,2; figures 4,5,7	1,2,4-15
X	US 2003/079743 A1 (GENOVA PERRY A ET AL) 1 May 2003 (2003-05-01) the whole document	1,2,4-15



Further documents are listed in the continuation of Box C.



See patent family annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

20 February 2006

Date of mailing of the international search report

22.03.2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Borowski, A

## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2006/000141

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 858 583 A (HALLWORTH ET AL) 7 January 1975 (1975-01-07) column 1, line 20 - line 38 column 1, line 51 - column 3, line 7 figures 1,4,5 -----	1,3,7-12
X	US 5 372 128 A (HABER ET AL) 13 December 1994 (1994-12-13) column 1, line 42 - column 2, line 3 column 2, line 35 - column 4, line 64 figures 2,4 -----	1,3,7-12

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB2006/000141

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16-24  
because they relate to subject matter not required to be searched by this Authority, namely:  
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy: a method of dispensing a powdered medicament to a patient.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2006/000141

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 3809084	A	07-05-1974	NONE	
US 2002088462	A1	11-07-2002	CA 2433799 A1 EP 1351734 A2 JP 2004527271 T WO 02053215 A2	11-07-2002 15-10-2003 09-09-2004 11-07-2002
US 3653380	A	04-04-1972	AT 330951 B AT 128471 A BE 762948 A1 CA 982005 A1 CH 536119 A DE 2106794 A1 DK 132012 B ES 194458 Y FR 2078678 A5 GB 1305172 A HK 13176 A JP 56001102 B MY 7776 A NL 7101065 A SE 381180 B ZA 7100007 A	26-07-1976 15-10-1975 16-08-1971 20-01-1976 30-04-1973 26-08-1971 13-10-1975 01-04-1975 05-11-1971 31-01-1973 19-03-1976 12-01-1981 31-12-1976 18-08-1971 01-12-1975 27-10-1971
US 2003079743	A1	01-05-2003	NONE	
US 3858583	A	07-01-1975	AU 6539674 A BE 811566 A1 CA 1048884 A1 CH 563168 A5 DE 2408791 A1 FR 2218905 A1 GB 1459426 A IT 1008929 B JP 1154491 C JP 50025092 A JP 57050505 B NL 7402230 A ZA 7400553 A	14-08-1975 26-08-1974 20-02-1979 30-06-1975 05-09-1974 20-09-1974 22-12-1976 30-11-1976 15-07-1983 17-03-1975 27-10-1982 28-08-1974 27-11-1974
US 5372128	A	13-12-1994	NONE	